BRAIN RESEARCH REVIEWS 67 (2011) 157–183

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BRAIN RESEARCH REVIEWS

Review

Interleukin-6, a mental cytokine

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ARTICLE INFO

Article history:
Accepted 8 January 2011
Available online 14 January 2011

Keywords:
IL-6
Central nervous system
Alzheimer's disease

ABSTRACT

Almost a quarter of a century ago, interleukin-6 (IL-6) was discovered as an inflammatory cytokine involved in B cell differentiation. Today, IL-6 is recognized to be a highly versatile cytokine, with pleiotropic actions not only in immune cells, but also in other cell types, such as cells of the central nervous system (CNS). The first evidence implicating IL-6 in brain-related processes originated from its dysregulated expression in several neurological disorders such as multiple sclerosis, Alzheimer's disease and Parkinson's disease. In addition, IL-6 was shown to be involved in multiple physiological CNS processes such as neuron homeostasis, astrogliogenesis and neuronal differentiation.

Abbreviations: 6-AN, 6-aminonicotinamide; Aβ, amyloid β; AD, Alzheimer's disease; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionate; AP-1, activator protein 1; APP, amyloid precursor protein; BDNF, brain-derived neurotrophic factor; cAMP, cyclic adenosine monophosphate; CBP, CREB binding protein; CCL, chemokine (C–C motif) ligand; CDKN2A, cyclin-dependent kinase inhibitor 2A; C/EBPβ, CCAAT/enhancer-binding protein β; CLC, cardiotrophin-like cytokine 1; CNS, central nervous system; CNTF, ciliary neurotrophic factor; CREB, cAMP response element binding protein; CSF, cerebrospinal fluid; CT-1, cardiotrophin 1; CXCL, chemokine (C–X–C motif) ligand; CXCR4, chemokine (C–X–C motif) 4 receptor; EAE, experimental autoimmune encephalomyelitis; EGF, epidermal growth factor; ERK, extracellular signal regulated kinase; GABA, γ-aminobutyric acid; GFAP, glial acidic fibrillary protein; GM-CSF, granulocyte macrophage colony stimulating factor; gp130, glycoprotein 130; grb2, growth factor receptor bound protein 2; HIV, human immune deficiency virus; HPA axis, hypothalamic–pituitary–adrenal axis; ICAM-1, intercellular adhesion molecule 1; ICV, intracerebroventricular; IFN-γ, interferon γ; IKK, inhibitor of NF-κB kinase; IL, interleukin; IL-6R, IL-6 receptor; iNOS, inducible nitric oxide synthase; JAK, janus kinase; JNK, c-Jun N-terminal kinase; LIF, leukemia inhibitory factor; LPS, lipopolysaccharide; LTP, long term potentiation; MAPK, mitogen-activated protein kinase; MBP, myelin basic protein; MD, major depression; MHC, major histocompatibility complex; MIA, maternal immune activation; MOG, myelin oligodendrocyte glycoprotein; MPP^+, 1-methyl-4-phenylpyridinium; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MS, multiple sclerosis; NF-κB, nuclear factor κ B; NGF, nerve growth factor; NMDA, N-methyl-D-aspartate; NO, nitric oxide; NPN, neuropoietin; NSE, neuronal specific enolase; NT, neurotrophin; OSM, oncostatin M; PD, Parkinson's disease; PI-3K, phosphatidylinositol-3 kinase; PMA, phorbol 12-myristate 13-acetate; PV, parvalbumin; SDF-1, stromal cell derived factor 1; SHP2, sarc homology region 2-domain containing tyrosine phosphatase 2; sIL-6R, soluble IL-6 receptor; SOCS-3, suppressor of cytokine signaling 3; SOS, son of sevenless; STAT, signal transducer and activator of transcription protein; SZ, schizophrenia; TGF-β, transformer growth factor β; Th, T helper cell; TLR, toll-like receptor; TMEV, Teiler murine encephalomyelitis virus; TNF-α, Tumor necrosis factor α; TNFR, TNF-α receptor; Treg, T regulatory cell; VCAM-1, vascular cell adhesion molecule 1; VLA-4, very late antigen-4; VNTR, variable number tandem repeat; WT, wild type

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0165-0173/$ – see front matter
doi:10.1016/j.brainresrev.2011.01.002

Multiple sclerosis
Excitotoxicity
Neurotrophic

The molecular mechanisms underlying IL-6 functions in the brain have only recently started to emerge. In this review, an overview of the latest discoveries concerning the actions of IL-6 in the nervous system is provided. The central position of IL-6 in the neuroinflammatory reaction pattern, and more specifically, the role of IL-6 in specific neurodegenerative processes, which accompany Alzheimer's disease, multiple sclerosis and excitotoxicity, are discussed. It is evident that IL-6 has a dichotomic action in the CNS, displaying neurotrophic properties on the one hand, and detrimental actions on the other. This is in agreement with its central role in neuroinflammation, which evolved as a beneficial process, aimed at maintaining tissue homeostasis, but which can become malignant when exaggerated. In this perspective, it is not surprising that 'well-meant' actions of IL-6 are often causing harm instead of leading to recovery.

Contents

1. Introduction

IL-6 was originally discovered as a factor produced by lymphocytes that stimulated the final maturation of B cells to antibody-producing cells (Hirano et al., 1986). Since its early characterization in the eighties (Haegeman et al., 1986; Hirano et al., 1985, 1986, 1987; May et al., 1986; Poupart et al., 1987; Van Damme et al., 1987; Yasukawa et al., 1987; Zilberstein et al., 1986), IL-6 has been implicated in an ever-growing array of processes, which include, among others, hematopoiesis, the acute phase response, liver regeneration, bone remodeling, metabolic processes and gliogenesis. IL-6 expression is furthermore dysregulated in diseases like atherosclerosis and asthma; in autoimmune diseases such as Crohn's disease, rheumatoid arthritis, diabetes and multiple sclerosis (MS); in different neurological disorders; and in various cancers such